UNITED S' ATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D C 20460

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OFFICE OF
PREVENTION PESTICIDES AN
TOXIC SUBSTANCES

MAY 6 1995

MEMORANDUM:

Subject: EPA ID # 067505-G: Ecto Flea & Tick Insecticide With IGR for Adult Dogs and Puppies Older than 8 Weeks - Review of Domestic Animal Safety Study (MRID # 43396408)

P.C. Nos.: 109701 & 129032
Tox. Chem. Nos.: 652BB
Submission No.: S475155
D.P. Barcode No.: D208877

From: Guruva B. Reddy, D.V.M., Ph.D. 5/16/95
Section 4
Toxicology Branch I
Health Effects Division (7509C)

To: Marion Johnson/Joseph Tavano
Project Manager 10
Registration Division (7505C)

Thru: John Doherty, Ph.D. 5/17/95
Acting Section Head
Section 4, Toxicology Branch I
Health Effects Division (7509C)

I. CONCLUSIONS:

The domestic animal safety study is inadequate and Unacceptable and does not satisfy the requirements, of a Series § 86-1 domestic animal safety study in adult dogs and puppies older than 8 weeks, because of violation of randomization procedures and inadequate number of animals; and lack of pertinent information such as bodyweight gain, food consumption etc., needed for evaluation of safety of the formulation were not collected or reported.

cc: Doherty

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II. ACTION REQUESTED:

ECTO Development Corporation, Excelsior Springs, MO., has submitted a domestic animal safety study in adult dogs and puppies older than 8 weeks, in support of registration of ECTO Flea & Tick Insecticide With IGR for the control of fleas, ticks and mosquitoes.

III. TOXICOLOGY BRANCH COMMENTS: The following study deficiencies were noted:

1. The study did not demonstrate a 3 - 5 fold safety factor between label usage rate and dermal reactions.

2. The animals selected for the study did not appear to be from a healthy stock. This is evidenced from the erythematous reactions in adults prior to application and presence of parvo virus, coccidial, bacterial and helminthic infections in puppies, which compromised study. Any or all treatments or prophylactic measures should be done during the acclimatization period.

3. Number of animals used in the study is inadequate. A minimum of 5/sex/age group, at 5 time the recommended dose level for twice the duration of intended use should be employed.

4. Data is lacking on bodyweight gains, food consumption, etc.. In the absence of which, safety of the treatments cannot be validated.

5. Dermal reactions in the vehicle treated were as severe as in the treated group. It appears the dermal reactions in this study were due to vehicle used in the formulation. Therefore, the registrant should consider changing vehicle for safer inactive ingredients.

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IV. STUDIES REVIEWED:

STUDY/CLASSIFICATION	TB-I COMMENTS
86-1 Domestic Animal Safety Study in Adult Dogs and Puppies older than 8 Weeks Ecto Dev. Corp., MO, and Calv, Inc. TX. Lab. Project #A-94-01F701-007; 09/15/94 MRID No.:43396408 **Core-Unacceptable**	In target animal safety study, adult mixed breed/Beagles and puppies were exposed to 0, Vehicle control (5X,, 1 (1X) or 5 (5X) ECTO Flea & Tick Insecticide With IGR (45% permethrin and 5% pyriproxyfen) at weekly intervals for a total of two applications (MRID No.: 43396408; Lab. Project # A-94-01-F701-007). At 1X and above, slight to severe dermal reactions were observed. In the vehicle treated group 5/6 animals exhibited dermal reactions (mild to severe) which were as severe as in the 5X treated group and lasted for 3 to 15 days. Dermal reactions in the vehicle treated group suggest that inactive ingredients in the formulation are irritating to the target animal. The study did not demonstrate a 3-5 fold safety factor between use as directed and dermal reactions. As conducted the study is inadequate and does not demonstrate the safety of the product. The study is classified as **Unacceptable** and does not satisfy the requirements, of a Series § 8.-1 domestic animal safety study in adult dogs and puppies older than 8 weeks of age.

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[86-1. ECTO Flea & Tick Insecticide With IGR - Adult dogs and puppies/1994]

Reviewed by: Guruva B. Reddy, D.V.M., Ph.D. 4/26/95
Section IV, Tox. Branch I (7509C)
Secondary Reviewer: John Doherty, Ph.D., Acting Section Head 5/17/95
Section IV, Tox. Branch I (7509C)

DATA EVALUATION REPORT

STUDY TYPE: Domestic Animal Safety Study - Dogs/86-1

	PC CODE No.	TOX. CHEM. No.
Permethrin	109701	652BB
Nylar	129032	-

MRID No.: 43396408

TEST MATERIAL: Ecto Flea & Tick Insecticide With IGR

SYNONYMS: Permethrin - 3-phenoxybenzyl-cis-(trans)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate

and

Nylar/pyriproxyfen - 2-[1-Mehtyl-2-(4-phenoxyphenoxy)ethoxy]pyridine

STUDY/PROJECT NUMBERS: 278-94-59/A-94-01-F701-007

SPONSOR: Ecto Development Corporation
Excelsior Springs, MO 64024

TESTING FACILITY: Ecto Development Corporation
Excelsior Springs, MO 64024

and

Calv, Inc. & CRC
Amarillo, TX 79118

TITLE OF REPORT: Study Report For The Target Animal Safety Evaluation Of Ecto Flea & Tick Insecticide With IGR on Dogs

AUTHORS: Robert G. Pennington
Bill C. Clymer

REPORT ISSUED: September 15, 1994

EXECUTIVE SUMMARY: In target animal safety study, adult mixed breed/Beagles and puppies were exposed to 0, Vehicle control (5X), 1 (1X) or 5 (5X) ECTO Flea & Tick Insecticide With IGR (45% permethrin and 5% pyriproxyfen) at weekly intervals for a

total of two applications (MRID No.: 43396408; Lab. Project # A-94-01-F701-007).

At 1X and above, slight to severe dermal reactions were observed during the study. In the vehicle treated group 5/6 animals exhibited dermal reactions (mild to severe) which were as severe as in the 5X treated group and lasted for 3 to 15 days. Dermal reactions in the vehicle treated group suggest that inactive ingredients in the formulation are irritating to the target animal. The study did not demonstrate a 3-5 fold safety factor between use as directed and dermal reactions.

The study is classified as **Unacceptable** and **does not satisfy** the requirements, § for a Series 86-1 domestic animal safety study in adult dogs and puppies older than 8 weeks of age.

A. MATERIALS:

1. **Test compound:** Flea and Tick Insecticide with IGR, Lot # A-93-01-F701-007; Vehicle, no batch number; Source: provided by the sponsor.

2. **Test animals:** Species: canine, Strain: Beagles and mixed breed mongrels, Age: 6 weeks to over 1 year, Weight: puppies - 2 to 13 lbs., mature dogs - 20 to 27 and 47 to 72 lbs.. Source: Auburn University, Auburn, Alabama, Cherri-Hill Kennel R & D and Martin Creek Kennels. All animals received from Martin Creek Kennels were acclimated for 15 days. The animals received from Auburn University and Cherri Hill Kennel R & D had been previously used as controls for another study were acclimated for 66 days. All animals received appropriate prophylactic treatments. <u>However, we question the soundness of selecting animals with pre-existing dermal conditions which interfere with the product's evaluation.</u>

B. STUDY DESIGN:

1. **Animal Assignment**

The animals were separated by sex, ranked by weight, and [redacted] assigned randomly to various study groups. <u>Random allocation was broken several times to balance</u>

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assignments by sex and weight. Following are the test groups:

DOSE	Adults		Puppies	
	♂	♀	♂	♀
Control	2	2	1	1
Vehicle	2	2	1	1
1 (1X)	2	4	1	2
5 (5X)	4	4	2	2

All animals were housed individually in stainless steel cages. Adults and puppies were housed in separate rooms, maintained at a temperature of 23°C with light: dark cycles of 13 hrs: 11 hrs. The adult dogs were fed Purina Grrravy Brand Dog Food®. Young puppies received Esbilac milk replacer mixed with Pro-Plan Dog Growth Formula® and the older puppies received Pro-Plan Growth Formula®. All animals received water ad libitum.

The animals were applied with Vehicle, 1X (1.5 mL/animal < 33 lbs and 3.0 mL/animal > 33 lbs) or 5X (7.5 mL/animal < 33 lbs and 15 mL/animal > 33 lbs) ECTO Flea & tick Insecticide With IGR on Days 0 and 7. In dogs < 33 lbs and all puppies, a single dose of 3.2 mL Vehicle, 1X or 5X formulation was applied between the shoulder blades. In case of dogs > 33 lbs, two doses of 3.2 mL Vehicle, 1X or 5X formulation each was applied between the shoulder blades and on the back at the tail base. Amount of vehicle applied should have been 7.5 mL in dogs < 33 lbs and puppies and 15 mL in the case of dogs > 33 lbs instead of 3.2 mL or multiple (2X) used in the study. However, due to inclusion of untreated concurrent controls in the study, the outcome of the study was not adversely effected. The study as designed is inadequate to demonstrate a 5 fold margin of safety for Ecto Flea & tick Insecticide With IGR for adult dogs and puppies older than 8 weeks, because of fewer number of animals. Further, the study as conducted did not follow the label recommended treatment at 3 week intervals, although it was a severe test of product's use.

2. **Statistics** - Data were not subjected to statistical analysis.

3. **QUALITY ASSURANCE:** A statement of quality assurance and a statement of GLP Compliance Monitoring Program were attached.

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C. **METHODS AND RESULTS:**

1. **Observations:**

Animals were observed for clinical signs of acute toxicity at 2, 4, and 6 hours after treatment on day 0 and 7; and twice daily thereafter. Detailed clinical evaluations were made every Monday, Wednesday and Friday, during the study.

Results:

One control (No. 11195) and one 5X (No. 11197) treated puppy died during the study; time and day of death was not reported. One puppy died of canine parvo virus infection and the second puppy died of multiple infections (coccidiosis, ascarids and bacterial infection). Infections in the puppy colony were confirmed on six stool samples which were positive for coccidia (5/6), ascarid and strongyloid-type ova (2/6). Three adult dogs (Nos. 5128, 8373 and 10346) in 5X group had pre-existing dermatitis or hair loss and one animal (No. 8373) had conjunctivitis. The animals were normal by treatment day 0. Following the 2nd application, the above three dogs and two additional dogs (Nos. 5147 and 11155) developed mild to severe signs of sustained dermal reactions lasting through the study period which are considered treatment-related. One puppy (No. 11197) had ataxia and was depressed after the second application (day 11) and died by day 20; and necropsy confirmed the death was due to coccidiosis with concurrent or sequential bacterial and ascarid infections. We concur with the conclusions. No signs of systemic toxicity were observed during the study. However, dermal reactions due to treatment were observed following the second treatment (day 7). <u>At 1X, 2 puppies (Nos. 11200 and 11205) starting day 11 after the second application showed slight reddening and mild rash on the abdomen and between the scapulas and lasted for two days and considered treatment related</u>. Adults treated in this group exhibited no dermal reactions.

In the 5X vehicle only treated group, two adult dogs (Nos. 9948 and 10544) had pre-existing dermatitis, which lasted throughout the experiment in one dog and cleared by day 4 in another dog. Following the second application the above dogs and an additional three animals (Nos. 5144, 5146, and puppy No.11198) exhibited mild to severe dermatitis lasting for 3 to 15 days.

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The reactions are considered due to the irritation potential of the vehicle. As formulated, the ECTO Flea & Tick Insecticide With IGR is not safe on adult dogs and puppies more than 8 weeks old. An alternate vehicle formulation should be considered for future experiments.

Untreated control dogs and puppies did not exhibit any abnormal signs.

2. **Body weight**

Animals were weighed on study day -3, 0 and 21.

Body weights were not analyzed or means tabulated. It appears from the raw data that the bodyweights were not affected.

3. **Food consumption**

Food consumption was not determined.

4. **Hematology and Serum Chemistries were not done.**

DISCUSSION:

This is a poorly conducted study. Following are the deficiencies:

1. Number of animals used in the study are inadequate. A minimum of 5/sex/age group, at 5 times the recommended dose level for twice the duration of intended use should be employed.

2. The animals selected for the study did not appear to be from a healthy stock. This is evidenced from the erythematous reactions in adults prior to application and presence of parvo virus, coccidial, bacterial and helminthic infections in puppies, which compromised study. Any or all examinations and treatments or prophylactic measures should be done during the acclimatization period.

3. Data is lacking on bodyweight gains, food consumption, etc.. In the absence of which, safety of the treatments cannot be validated.

4. Randomization was not strictly followed. To equally distribute the sexes, age and bodyweight, the codes were violated.

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5. Dermal reactions in the vehicle treated groups were as severe as in the treated group. It appears the dermal reactions in this study were due to vehicle used in the formulation. Therefore, the registrant should consider changing the vehicle for safer inactive ingredients.

The study did not demonstrate a 3-5 fold safety factor between use as directed and dermal reactions.

The study is classified as **Unacceptable** and **does not satisfy** the requirements, for a Series § 86-1 domestic animal safety study for this product in adult dogs and puppies older than 8 weeks of age.

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Final: 4/28/95

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